Application No.: RCE of 09/914451 Docket No.: PVZ-006USRCE

AMENDMENTS TO THE CLAIMS

Listing of Claims

This listing of the claims will replace all prior versions, and listings, of claims in this application.

1-59. (Cancelled)

- 60. (Currently Amended) A method of identifying compounds that bind to a leukotriene A_4 (LTA₄) hydrolase comprising the amino acid sequence of SEQ ID NO:1, the method comprising the steps of:
- (a) crystallizing a purified LTA₄ hydrolase <u>in the presence of bestatin</u> to form <u>a co-crystal of</u> [[an]] LTA₄ hydrolase <u>and bestatinerystal</u>, wherein crystallization is performed [[as]]<u>by</u> liquid_liquid diffusion in a capillary using equal volumes of a buffer: enzyme solution consisting of:
- i) a buffer solution consisting of 28% PEG8000, 0.1 M Na-acetate, 0.1 M imidazole at a pH of 6.8 and with 5 mM YbCl₃ as an additive; and
- ii) an enzyme solution consisting of 5 mg/ml LTA₄ hydrolase comprising the amino acid sequence of SEQ ID NO:1 in 10 mM Tris-HCl at a pH of 8, supplemented with 1 mM bestatin;

wherein the crystallization results in a LTA₄ hydrolase crystal having the space group P2₁2₁2 and the unit cell dimensions a=67.59 Å, b=133.51 Å, and c=83.40 Å and α = β = γ =90°;

- (b) determining the atomic coordinates of said LTA₄ hydrolase crystal; and
- (c) screening the atomic coordinates of a set of candidate compounds against the atomic coordinates of said LTA₄ hydrolase crystal obtained in step a) to identify compounds that bind to the LTA₄ hydrolase;

wherein the crystallization results in a LTA₄ hydrolase crystal having the space group P21212 and the unit cell dimensions a=67.59 Å, b=133.51 Å, and c=83.40 Å and wherein α = β = γ =90°.

61. (**Previously Presented**) The method of claim 60, wherein the LTA₄ hydrolase is purified by adsorption chromatography on hydroxyapatite and anion-exchange chromatography.

62-67. (**Cancelled**)

Application No.: RCE of 09/914451 Docket No.: PVZ-006USRCE

68. (**Previously Presented**) The method of claim 60, wherein the atomic coordinates of said LTA_4 hydrolase crystal correspond to the atomic coordinates defining atom 1 to atom 4876 as set forth in Table 9.

69. (Cancelled)

- 70. (**Currently Amended**) A method of designing an inhibitor or <u>an</u> agonist of LTA₄ hydrolase comprising the amino acid sequence of SEQ ID NO:1, the method comprising the steps of:
- (a) crystallizing a purified LTA₄ hydrolase <u>in the presence of bestatin</u> to form a <u>co-</u>crystal <u>of LTA₄ hydrolase and bestatin</u> and thereafter determining its <u>three dimensional</u> conformational structure, wherein <u>the crystallization</u> is performed [[as]]<u>by</u> liquid_liquid diffusion in a capillary using equal volumes of a buffer: enzyme solution consisting of:
- i) a buffer solution consisting of 28% PEG8000, 0.1 M Na-acetate, 0.1 M imidazole at a pH of 6.8 and with 5 mM YbCl₃ as an additive; and
- ii) an enzyme solution consisting of 5 mg/ml LTA₄ hydrolase comprising the amino acid sequence of SEQ ID NO:1 in 10 mM Tris-HCl at a pH of 8, supplemented with 1 mM bestatin;

wherein the crystallization results in a LTA₄ hydrolase crystal having the space group $P2_12_12$ and the unit cell dimensions a=67.59 Å, b=133.51 Å, and c=83.40 Å and α = β = γ =90°; and

iii) determining the atomic coordinates of said LTA₄ hydrolase crystal;

- (b) identifying at least one <u>potential inhibitor or agonist compound</u> that is at least in part complementary to the LTA₄ hydrolase by the use of the <u>atomic coordinates of the LTA₄</u> hydrolase crystalconformational structure of the crystal complex obtained in step a);
- (c) soaking the <u>co-</u>crystallized LTA₄ hydrolase obtained in step a) with a solution of a <u>compoundthe potential inhibitor or agonist</u> identified in step b) to obtain a complex of the crystal of said LTA₄ hydrolase and said <u>potential inhibitor or agonist compound</u>; and
- (d) <u>determining the atomic coordinates performing X ray crystallography</u> of the crystal complex of <u>said LTA</u>₄ hydrolase and said <u>inhibitor or agonist in step (c)</u> compound to determine the structure thereof, thereby identifying the <u>potential inhibitor or agonist</u> as an inhibitor or agonist of LTA₄ hydrolase;

Application No.: RCE of 09/914451 Docket No.: PVZ-006USRCE

wherein the crystallization results in a LTA₄ hydrolase crystal having the space group P21212 and the unit cell dimensions a=67.59 Å, b=133.51 Å, and c=83.40 Å and wherein $\alpha=\beta=\gamma=90^{\circ}$.

71. (**Previously Presented**) The method of claim 70, wherein the LTA₄ hydrolase is purified by adsorption chromatography on hydroxyapatite and anion-exchange chromatography.

72-75. (Cancelled)

76. (**Currently Amended**) The method of claim 70, wherein the atomic coordinates of said LTA₄ hydrolase crystal <u>in step (a)</u> correspond to the atomic coordinates defining atom 1 to atom 4876 as set forth in Table 9.

77. (Cancelled)

- 78. (**Currently Amended**) The method of claim 70, further comprising the step of refining the structure of the inhibitor or agonistsaid compound obtained in step d) via computer modeling using data obtained in step d) via computer modeling and using this refined datafrom the X-ray erystallography in step d) and repeating steps b)-d).
- 79. (**Previously Presented**) The method of claim 70, wherein the complex obtained in step c) comprises bestatin.

80-86. (**Cancelled**)